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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,685	MODEL ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-22 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-22 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on January 21, 2011 is acknowledged and has been entered. Claims 1, 11, 18 have been amended. Claims 2, 23-30, 32-39 have been canceled. Claims 1, 3-22 and 31 are pending.

Claims 1, 3-22 and 31 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

Previous Grounds of Rejection – adjusted to address amendment to the claims

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 10-11, 16-17 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. (Cancer Reseach, 1997, 57:2619-2622) in view of Adorjan et al. (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9, IDS reference).

With regard to claim 1, Wong teaches a method for producing DNA, wherein a methylation analysis is used, comprising the steps of:

a) performing a genome-wide amplification on genomic DNA (p. 2619, col. 2, where whole genome amplification was carried out with PEP amplification, p. 2620, col. 1, where the PEP products are used in MSP PCR analysis);

b) using the amplificates generated in step a) as a non-methylated standard in the methylation analysis over a linear range (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction; Figure 1A, where there are unmethylated controls and methylated controls)

With regard to claim 3, Wong teaches an embodiment of claim 1 wherein the amplification methods performed are PEP, DOP-PCR or linker PCR (p. 2619, col. 2, where whole genome amplification was carried out with PEP amplification, p. 2620, col. 1).

With regard to claim 10, Wong teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by methylation- specific ligation methods, MSP, Heavy Methyl or MethyLight (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction, p. 2620. col. 1, where methylation specific PCR is described, see Figure 1).

With regard to claim 11, Wong teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by primer extension (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction, p. 2620. col. 1, where methylation specific PCR is described, see Figure 1).

With regard to claim 16, Wong teaches an embodiment of claim 1 wherein the methylation analysis is performed for the diagnosis of cancer diseases or other diseases associated with a modification of the methylation status (Abstract, Figure 1, Table 1, where the technique was used to detect methylation in cancer samples).

With regard to claim 17, Wong teaches an embodiment of claim 1 wherein the methylation analysis is performed for the prognosis of desired or undesired effects of drugs and for the differentiation of cell types or tissues, or for the investigation of the cell differentiation (Abstract, Figure 1, Table 1, where the technique was used to detect methylation in cancer samples).

With regard to claim 31, Wong teaches an embodiment of claim 1, wherein the genome-wide amplification is performed by exclusively using nucleotides or nucleotide triphosphates, respectively, which are non-methylated (p. 2620, col. 1, where the genome-wide amplification is carried out using non-methylated nucleotides).

Claims 18-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Adorjan et al. (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9, IDS reference). Adorjan teaches microarray based DNA methylation analysis (Abstract).

With regard to claim 18, Adorjan teaches a method for the determination of methylation rates of DNA samples by means of microarrays containing CG and TG oligomers, comprising the steps of:

a) hybridizing the arrays with two calibration standards, which have defined methylation rates, wherein one calibration standard comprises non-methylated DNA and the other calibration standard comprises specifically methylated DNA (p. 2, col. 2, where for each analyzed CpG position, CG and TG oligomers are spotted onto a glass array; Table 1, p. 3, col. 2, where DNA fragments of known methylation were mixed in different ratios and hybridized to the array, Figure 1 legend, see A) where methylation statuses of 0%, 66%, 33%, 100% include non-methylated DNA (0%) and specifically methylated DNA (100%));

b) using the hybridization values of step a) to determine a calibration curve for use as a suitable method of calculation (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 2); and

c) determining the actual methylation rates of the investigated DNA samples by using this prepared calibration curve (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 2).

With regard to claim 19, Adorjan teaches an embodiment of claim 18, wherein the two calibration standards have methylation rates of 0% and 100%, respectively (Figure 1, and legend, where the standards have methylation rates between 0 and 100%).

With regard to claim 20, Adorjan teaches an embodiment of claim 18, wherein more than two calibration standards are used, which have different methylation rates (Figure 1, and legend, where the standards have methylation rates between 0 and 100%).

With regard to claim 21, Adorjan teaches an embodiment of claim 18, wherein the actual methylation rates are determined in a multi-stage calculation process, comprising the steps of:
a) normalizing the hybridization values, wherein methylation signals are determined (p. 3, col. 1, where the statistical analysis is described, including the algorithms used, p. 3, col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend),
b) normalizing the methylation signals with the aim of variance stabilization (p. 3, col. 1, where the signals are normalized using a Support Vector Machine (SVM) and Sequential Minimal Optimization Algorithm, p. 3 col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend), and
c) determining the absolute methylation rates by using the calibration standards and a suitable maximum likelihood algorithm (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 1-2, see above; see legend to Figure 3 legend, where hypermethylation is depicted as red, mean methylation is black and hypomethylation is green).

With regard to claim 22, Adorjan teaches an embodiment of claim 21, further comprising a step prior to step a) wherein the hybridization values are corrected for the background noise inherent in the measurement method (p. 3, col. 1, where the signals are normalized using a

Support Vector Machine (SVM) and Sequential Minimal Optimization Algorithm, p. 3 col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Apgar et al. (Human Immunology, 2003, 64(10), Suppl. 1, p. S86, Abstract). Schatz teaches methylation analysis using mass spectrometry analysis (Abstract).

With regard to claim 4, Apgar teaches an embodiment of claim 1, wherein the amplification method performed is a multiple displacement amplification (MDA) (Abstract, lines 4-6, where the amplification is by MDA).

With regard to claim 5, Apgar teaches an embodiment of claim 4, further comprising using a phi 29 polymerase (Abstract, line 5).

With regard to claim 6, Apgar teaches an embodiment of claim 4, further comprising using a commercially available kit (Abstract, line 10).

With regard to claim 7, Apgar teaches an embodiment of claim 6, wherein the commercially available kits are "GenomiPhi" (Amersham Biosciences) or "Repli-g" (Molecular Staging) (Abstract, line 10).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Schatz to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success. As taught by Apgar, "replicate aliquots of dilute DNA were amplified by MDA using a GenomiPhi kit" (Abstract, line 10). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Schatz to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Adorjan et al. (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9).

Wong teaches all of the limitations of claims 1, 3, 10-11, 16-17 and 31. Wong does not teach the use of a microarray. Adorjan teaches microarray based DNA methylation analysis (Abstract).

With regard to claim 12, Adorjan teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by an amplification and a hybridization of the amplificates at oligomer microarrays (p. 2, col. 2, where for each analyzed CpG position, CG and TG oligomers are

spotted onto a glass array; Table 1, p. 3, col. 2, where DNA fragments of known methylation were mixed in different ratios and hybridized to the array, Figure 1; see also p. 2, col. 2, where bisulfite conversion and amplification are discussed.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the analysis of methylation using microarrays as taught by Adorjan to arrive at the claimed invention with a reasonable expectation for success. As taught by Adorjan, "We have developed the first microarray-based technique which allows genome-wide assessment of selected CpG dinucleotides as well as quantification of methylation at each site. Several hundred CpG sites were screened in 76 samples from four different human tumour types and corresponding healthy controls. Discriminative CpG dinucleotides were identified for different tissue type distinctions and used to predict the tumour class of as yet unknown samples with high accuracy using machine learning techniques". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the analysis of methylation using microarrays as taught by Adorjan to arrive at the claimed invention with a reasonable expectation for success.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Tost et al. (Nucleic Acids Research, 2003, 31(9):e50, p. 1-10).

With regard to claim 13, Tost teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which

methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by means of a multiplex PCR (p. 6, col. 2, where the CpG methylation was detected using multiplex primer extension).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success. As taught by Tost, "Calibration curves were recorded for simplex, duplex and triplex analysis. For multiplex analysis only extension primers were chosen that did not overlap in their sequence". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success.

Claims 14-15 rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Guilleret et al. (Int. J. Cancer, 2002, 101, p. 335-341). Wong teaches detection of promoter methylation in p16 in cancer (Abstract).

With regard to claim 14, Guilleret teaches an embodiment of claim 1 wherein a mixture of methylated and non-methylated DNA is used as a standard (Figure 1, where mixtures of methylated and unmethylated plasmid DNA was used as a standard; see also p. 336, col. 1, 'plasmids' heading, where the mix of methylated and unmethylated is discussed).

With regard to claim 15, Guilleret teaches an embodiment of claim 1 wherein several mixtures of methylated and non-methylated DNA with different shares of methylated and non-methylated DNA are used as a standard (Figure 1, where mixtures of methylated and unmethylated plasmid DNA was used as a standard and where the mix included 0%, 50% and 100% methylation; see also p. 336, col. 1, 'plasmids' heading, where the mix of methylated and unmethylated is discussed).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the mixtures of methylated and non-methylated DNA as a standard as taught by Guilleret to arrive at the claimed invention with a reasonable expectation for success. While Wong teaches the use of methylated controls and unmethylated controls, Wong does not teach mixing the controls for detection of different types of methylation, such as differential methylation. As taught by Guilleret, "Unmethylated and methylated plasmids were mixed at different ratios. The bisulfite modification was performed on fully methylated and unmethylated plasmids as well as on different mixes" (p. 336, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the mixtures of methylated and non-methylated DNA as a standard as taught by Guilleret to arrive at the claimed invention with a reasonable expectation for success to achieve reliable detection of methylation.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dean et al. (US Patent 6,617,137 September 2003) teaches methods of whole genome amplification.

Response to Arguments

Applicant's arguments filed January 21, 2011 have been fully considered but they are not persuasive.

Applicant traverses the rejection of claims 1, 3, 10-11, 16-17 and 31 as being anticipated by Wong. Applicant argues that Wong "fails to teach or suggest using amplificates of genomic DNA 'as a non-methylated standard in the methylation analysis over a linear range" (p. 6 of remarks) and emphasizes non-methylated standard and linear range. Applicant then argues "the controls in Wong "does not provide an enabling disclosure for this feature of the currently amended claim 1" and "Wong only teaches the use of PEP to amplify genomic DNA for about 60 folds in order to reduce the amount of genomic DNA needed for subsequent assays, where the claimed invention can perform more than 5,000 fold genome-wide amplification" (p. 7 of remarks).

These arguments have been considered, but are not persuasive. Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. While applicant's arguments regarding the asserted lack of enabling disclosure of non-methylated standards for analysis over a linear range

are noted, it is noted in response that Applicant has not really done more than make a general assertion that the Wong reference fails to teach these features. Applicant has not specifically pointed out where Wong does not teach a non-methylated standard for analysis over a linear range. Furthermore, it is noted that neither Applicant's remarks or the specification provide a clear basis or explanation as to what "analysis over a linear range" would entail or how it would distinguish over the Wong reference. In the absence of more specific argument with such explanation, the arguments are viewed as wholly unpersuasive and the rejection is maintained. As noted above, Wong clearly teaches an unmethylated standard and analysis of methylation status following whole genome amplification by PEP amplification. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., fold amplification of the whole genome amplification) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant traverses the rejection of claims as being anticipated by Adorjan. Applicant argues that claim 18 has been amended and "Adorjan does not disclose or suggest these features of the currently amended claim 18" and points to their own specification as evidence that "Adjoran et al. is limited to 'relative' estimation of methylation analysis". Applicant contrasts this with the "measurement of 'absolute' methylation rates or 'true methylation rates" (p. 8 of remarks).

These arguments have been considered, but are not persuasive. While Applicant's argument has been considered, the arguments are not persuasive. Adorjan, as noted in the rejection as amended specifically teaches the generation of a calibration curve using methylation standards that include non-methylated DNA and specifically methylated DNA (see legend to Figure 1A, where methylation status of 0% and 100% represent unmethylated and fully methylated DNA respectively). Furthermore, while Applicant may argue in their specification that Adjoran represents relative methylation analysis, Applicant's discussion of the technique of absolute methylation analysis relies upon the generation of a calibration curve (see p. 8 of specification). Measurements were taken for each of the samples of known methylation standards referenced in Figure 1A and where calculated and calibrated in Figure 1B and analyzed by a Support Vector Machine. In the absence of further explanation how calibration standards used in the same way as claimed does not provide the same end result of absolute methylation rates, Applicant's arguments are not persuasive and the rejection is maintained.

Applicant traverses the rejection of claim 12 as being obvious over Wong in view of Adorjan. Applicant argues "neither Wong nor Adorjan discloses or suggests each and every element of the current amended claim 1" and "therefore not claim 12 either" (p. 10 of remarks).

These arguments have been considered, but are not persuasive for the same reasons as asserted above regarding Wong and regarding Adorjan. As argued above, Wong does provide explicit teaching of amplification of genomic DNA, even if the genomic DNA is bisulfite-modified before amplification. Further, Wong teaches the use of these samples as standards in

methylation analysis. Therefore, for at least these reasons, Applicant's arguments are not persuasive and the rejections are maintained.

Applicant traverses the rejection of claim 13 as obvious over Wong in view of Tost; rejection of claim 14-15 as obvious over Wong in view of Guilleret; and the rejection of claims 4-7 as obvious over Wong in view of Apgar. Applicant again reiterates the same arguments as asserted above regarding Wong. These arguments are not persuasive for the same reasons as asserted above and the rejection is maintained.

Conclusion

No claims are allowed. All claims stand rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Primary Examiner, Art Unit 1637

SKM